PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference C1-A0504P	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/JP2006/306821	International filing date *(day/month/year)* 31 March 2006 (31.03.2006)	Priority date *(day/month/year)* 08 April 2005 (08.04.2005)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 09 October 2007 (09.10.2007)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yoshiko Kuwahara e-mail: pt07.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	
Applicant's or agent's file reference C1-A0504P	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2006/306821	31.03.2006	08.04.2005

International Patent Classification (IPC) or both national classification and IPC

Applicant
CHUGAI SEIYAKU KABUSHIKI KAISHA

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP	Date of completion of this opinion	Authorized officer
Facsimile No.		Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2006/306821

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ the translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rule 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☒ in electronic form

   c. time of filing/furnishing

      ☒ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
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Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 15, 18, 28

because:

☒ the said international application, or the said claims Nos. 15, 18 relate to the following subject matter which does not require an international search (*specify*):

The subject matters of the above-mentioned claims relate to a method for treatment by therapy of the human body or a method for diagnosis.

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 28 are so unclear that no meaningful opinion could be formed (*specify*):

What is specifically encompassed in the "bispecific antibody" of the above-mentioned claims and what is not encompassed therein is not at all clear. So, the descriptions of the above-mentioned claims are extremely unclear. Therefore, no meaningful comments can be presented for the above-mentioned claims.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. 15, 18, 28

☐ a meaningful opinion could not be formed without the sequence listing: the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

Reference document:
JP, 2001-523971, A (Genentech, Inc.), 27 November, 2001 (27.11.01), & WO, 98/50431, A2, & EP, 979281, A2, & US, 2003/207346, A1

Since the above document describes a multi-specific antibody, wherein antibody L-chain parts contain a common sequence, it is not considered that there is a technical relationship including a same "special technical feature" just because antibody L-chain parts are the same.

Therefore, the subject matters of claims 1-14, 16, 17 and 19 and the subject matters of claims 20-27 are not considered to be a group of inventions so linked as to form a single general inventive concept, and so this application is considered to encompass two inventions.

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☐ all parts

   ☒ the parts relating to claims Nos. 1-14, 16, 17, 19

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/JP2006/306821

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-14, 16, 17, 19	YES
	Claims		NO
Inventive step (IS)	Claims	1-14, 16, 17, 19	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-14, 16, 17, 19	YES
	Claims		NO

2. Citations and explanations:

Document 1: JP, 2003-509049, A (Baxter AG), 11 March, 2003 (11.03.03), & WO, 2001/019992, A2, & EP, 1220923, A2, & US, 2005/196397, A1
Document 2: Okubo Y., et al., The production and characterization of four monoclonal antibodies to human factor X., J. Nara Med. Ass., 1987, vol. 38, no. 1, pages 20-28
Document 3: Hoad PB, et al., Characterization of monoclonal antibodies to human factor X.Xa: Initial observations with a quantitative ELISA procedure, J. Immunol. Methods, 1991, vol. 136, no. 2, pages 269-278
Document 4: Lapan KA, et al., Interaction of the A1 subunit of factor VIIIa and the serine protease domain of factor X identified by zero-length cross-linking, Thromb. Haemost., 1998, vol. 80, no. 3, pages 418-422
Document 5: Brinkman HJ, et al., Phospholipid-binding domain of factor VIII is involved in endothelial cell-mediated activation of factor X by factor IXa, Arterioscler. Thromb. Vasc. Biol., 2002, vol. 22, no. 3, pages 511-516
Document 6: JP, 2001-523971, A (Genentech, Inc.), 27 November, 2001 (27.11.01), & WO, 98/50431, A2, & EP, 979281, A2, & US, 2003/207346, A1
Document 7: Segal DM, et al., Introduction: bispecific antibodies, J. Immunol. Methods, 2001, vol. 248, nos. 1 and 2, pages 1-6

Claims 1-14, 16, 17 and 19

Document 1 describes a monoclonal antibody which can replace the function of blood clotting factor VIII (hereinafter, referred to simply as "factor VIII" by omitting "blood coagulation" as for each blood clotting factor), wherein the monoclonal antibody is for factors IX and IXa. Furthermore, document 1 describes that a conjugate of factors VIII and IXa activates factor X. Furthermore, document 1 suggests that the monoclonal antibody is rendered bispecific.

Document 2 describes a monoclonal antibody for factor X, wherein the monoclonal antibody does not inhibit the blood clotting activity of factor X (NMC-X/4). Furthermore, document 3 describes a monoclonal antibody for factor X as well.

Documents 4 and 5 describe that a conjugate of factors VIII and IXa activates factor X.

Furthermore, as described in documents 6 and 7, preparation of a bispecific antibody is considered to have been well known to a person skilled in the art before the priority date of this application. Furthermore, document 6 describes a multi-specific antibody, wherein antibody L-chain parts are composed of a common sequence.

However, even in view of all these documents, it is not considered that a person skilled in the art could have conceived that a multi-specific antibody including a first domain recognizing factor IX and/or factor IXa and a second domain recognizing factor X can replace the function of blood clotting factor VIII. Namely, the subject matters of the above-mentioned claims are considered to exhibit a remarkable effect that could not have been conceived of by a person skilled in the art

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

from documents 1-7 and common technical knowledge prevailing before the priority date of this application.

Therefore, the subject matters of the above-mentioned claims appear to be novel and to involve an inventive step, since they could not have been easily arrived at by a person skilled in the art from documents 1-7 and common technical knowledge prevailing before the priority date of this application.